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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/609,279	06/30/2000	Sharat Singh	ACHBI.044.01US	2587

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/609,279	SINGH ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status

Applicant correctly notes that the previous action was a NON-final action. The notation on the form that the action was final was in error. The current action is, however, a final rejection of the claims.

Claims 1-29 are pending.

Claims 1-24 are rejected.

Claims 25-29 are withdrawn from consideration.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Double Patenting

1. The double patenting rejection is withdrawn in view of the terminal disclaimer over the copending application.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-8, 10-16, and 18-24 are rejected under 35 U.S.C. 102(b) as being anticipated by O'Neill et al (WO 98/14610).

O'Neill teaches a method of multiplex sequencing (see page 12) on nucleic acids ranging from PCR products to chromosomal DNA (necessarily greater than 2 Kb) (page 13, lines 3-6) comprising the steps:

a) combining under hybridizing conditions a target nucleic acid sequence and primer reagents (page 12, lines 16-19), where the primer reagents have (i) a first sequence part homologous to the target nucleic acid (page 8, lines 1-21) and (ii) a second sequence part homologous to a capture reagent(page 8, lines 22-30) and where each second sequence part is different (page 12, lines 2-10) and O'Neill expressly identifies the embodiment where each set has different recovery tags (page 14, line 16),

b) extending said primers duplexed with target with a polymerase in the presence of dNTPs and at least one terminator nucleotide, to add said dNTPs and said at least one terminator nucleoitde to said primer reagent to extend said primer reagent with a sequence complementary to the DNA target sequence to form extended primer sequences, using at least two different terminator nucleotides (page 12, lines 13-30 and page 14, lines 3-8),

c) dissociating said extended primer sequence from homologous sequences (page 16, lines 13-32 and page 13, line 28, denaturing the primed template),

d) repeating steps a)-c) (page 13, lines 17-31),

e) combining said extended primer sequences with capture reagents homologous to the capture sequence attached to a bead sequestering reagent (page 16, lines 13-33 and page 20, line 19 to page 21, line 32),

f) releasing sequentially subsets of said primer reagents by increasing the stringency conditions which may include temperature, denaturing agents, (note that going from no stringency conditions to particular conditions is a stepwise change which releases a subset of primer reagents and that page 19, lines 2-3 expressly indicate that different recovery tags may be released by different releasing procedures) (page 17, line 32 to page 20, line 18),

g) analysing by electrophoresis said extended primers to determine the sequence of said target DNA (page 32, example 3).

O'Neill expressly teaches primer reagents with identifiers such as fluorescent labels (page 15, lines 1-17) which labels affect mobility in an electrophoresis medium.

O'Neill expressly teaches the use of biotin-avidin binding pairs for capture (page 7, lines 1-6).

O'Neill expressly teaches hinged primers with a non-replicable moiety between the sequence parts (page 24, lines 23-33).

O'Neill expressly teaches the use of four different vessels with four different sequencing reactions with four different chain terminators (page 14, lines 9-29).

O'Neill expressly teaches the use of a strand cleaving reagent to modify, by cleavage, the primer reagents (page 19, lines 11-30).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-16 and 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Neill et al (WO 98/14610) in view of Matthews et al (Anal. Biochem. 169 (1988) 1-25).

O'Neill teaches a method of multiplex sequencing (see page 12) on nucleic acids ranging from PCR products to chromosomal DNA (necessarily greater than 2 Kb) (page 13, lines 3-6) comprising the steps:

a) combining under hybridizing conditions a target nucleic acid sequence and primer reagents (page 12, lines 16-19), where the primer reagents have (i) a first sequence part homologous to the target nucleic acid (page 8, lines 1-21) and (ii) a second sequence part homologous to a capture reagent(page 8, lines 22-30) and where each second sequence part is different (page 12, lines 2-10) and O'Neill expressly identifies the embodiment where each set has different recovery tags (page 14, line 16),

b) extending said primers duplexed with target with a polymerase in the presence of dNTPs and at least one terminator nucleotide, to add said dNTPs and said at least one terminator nucleoitde to said primer reagent to extend said primer reagent with a

sequence complementary to the DNA target sequence to form extended primer sequences, using at least two different terminator nucleotides (page 12, lines 13-30 and page 14, lines 3-8)

c) dissociating said extended primer sequence from homologous sequences (page 16, lines 13-32 and page 13, line 28, denaturing the primed template)

d) repeating steps a)-c) (page 13, lines 17-31),

e) combining said extended primer sequences with capture reagents homologous to the capture sequence attached to a bead sequestering reagent (page 16, lines 13-33 and page 20, line 19 to page 21, line 32),

f) releasing sequentially subsets of said primer reagents by increasing the stringency conditions which may include temperature, denaturing agents, (note that going from no stringency conditions to particular conditions is a stepwise change which releases a subset of primer reagents and that page 19, lines 2-3 expressly indicate that different recovery tags may be released by different releasing procedures) (page 17, line 32 to page 20, line 18),

g) analysing by electrophoresis said extended primers to determine the sequence of said target DNA (page 32, example 3).

O'Neill expressly teaches primer reagents with identifiers such as fluorescent labels (page 15, lines 1-17) which labels affect mobility in an electrophoresis medium.

O'Neill expressly teaches the use of biotin-avidin binding pairs for capture (page 7, lines 1-6).

O'Neill expressly teaches hinged primers with a non-replicable moiety between the sequence parts (page 24, lines 23-33).

O'Neill expressly teaches the use of four different vessels with four different sequencing reactions with four different chain terminators (page 14, lines 9-29).

O'Neill expressly teaches the use of a strand cleaving reagent to modify, by cleavage, the primer reagents (page 19, lines 11-30).

O'Neill does not appear to teach the embodiment where the capture is solution based followed by binding to the solid support.

Matthews teaches solution hybridization followed by capture of the hybrids onto a solid support (page 17, figure 10).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize solution hybridization as taught by Matthews in the method of O'Neill since Matthews states "Solution hybridization is inherently faster than solid-phase hybridization (page 17, column 1)". An ordinary practitioner would have been motivated to use solution hybridization as taught by Matthews in the method of O'Neill in order to speed up the hybridization reaction. While O'Neill does not teach multiplexing using 50 genotypes, an ordinary practitioner would have recognized, at the time of invention, that the suggestion on page 10 to multiplex the method and perform 12 different sequences represents 48 different extension reactions which is within the range of routine optimization of 50. As the court stated in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

An ordinary practitioner would have been able to perform routine optimization of the number of extension products to utilize the number desired.

7. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Neill et al (WO 98/14610) in view of Matthews et al (Anal. Biochem. 169 (1988) 1-25) and further in view of Koster et al (U.S. Patent 5,928,906)

O'Neill in view of Matthews teaches the limitations of claims 1-16 and 18-24 as discussed above. O'Neill in view of Matthews do not teach the use of nucleic acids as mobility tags.

Koster teaches the use of a variety of mobility tags for multiplexing purposes and expressly teaches modifying the lengths of nucleic acids as a mobility tag, stating " "Multiplexing" can be achieved either by the sequence itself (composition or length) or by the introduction of mass-modifying functionalities into the primer oligonucleotide. Such multiplexing is particularly useful in conjunction with mass spectrometric DNA sequencing or mobility modified gel based fluorescence sequencing. (Column 9, lines 54-60)."

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of O'Neill in view of Matthews with the nucleic acid and mass modifying mobility modifiers of Koster since Koster teaches that these modifiers are particularly useful in multiplexing for DNA sequencing purposes.

Response to Arguments

8. Applicant's arguments filed April 4, 2002 have been fully considered but they are not persuasive.

Applicant argues that O'Neill does not teach the use of sequentially increasing the stringency conditions for release. This argument is not persuasive for the reasons given in the rejection. First, the claim simply requires "releasing sequentially" (see claim 1). As noted in the rejection a change from no stringency conditions to particular conditions is a stepwise change which releases a subset of primer reagents. That is, a step in which the support is washed will remove some reagents followed by a stringent elution

will remove the remainder of the attached reagent. This is a two step procedure and is illustrated in example 3 at page 32. Second, while O'Neill clearly prefers simultaneous release, MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because O'Neill had a preferred embodiment of simultaneous release, this embodiment does not constitute a teaching away from the expressly indicated embodiment that "Different recovery tags may be released by the same or different releasing procedures in given embodiments of the invention. Preferably all recovery tags in a given embodiment of the invention are released by the same procedure (see page 19, lines 2-4)". This statement, while expressly preferring the use of a single procedure, clearly recognizes that different releasing procedures may be used in a single assay. The use of different releasing procedures would inherently and necessarily result in stepwise sequential release, since a first procedure would be performed followed by a second or more procedures. Therefore, O'Neill remains properly anticipatory to the claimed invention.

Applicant argues that the 103 rejections should be withdrawn because of O'Neill is not properly an anticipatory reference based on the arguments addressed above. Since these arguments were not found persuasive, the rejection is maintained.

Applicant correctly notes that the previous action could not be final and correctly noted that the examiner did not insert the final form paragraphs. When the action was prepared for mailing in the office, the final rejection box was inadvertently checked. The current action is, however, correctly made final as the second action repeating the same exact rejection regarding the same claims.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers

for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634

July 2, 2003